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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/632,149	CUTHBERTSON, R. ANDREW	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/31/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 23-24 and new claims 25-27 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-24 and new claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the previous Office Action dated 11/06/02 (pages 3-9).

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are drawn to a method of treating an ocular wound or an ocular wound after surgery, said method comprising directly contacting an exogenous nucleic acid and an ocular cell *in situ* under conditions permissive for the direct uptake of said

exogenous nucleic acid by said ocular cell, whereby said exogenous nucleic acid is expressed in said ocular cell, the same method wherein said exogenous nucleic acid encodes transforming growth factor β (new claim 25), or wherein the ocular wound is a corneal epithelial wound (new claim 26), preferentially the corneal epithelial wound is a corneal ulceration (new claim 27).

The specification teaches by exemplification showing that upon superficial epithelial debridement (surgical removal of superficial epithelial cells) and topical application of a recombinant replication-defective adenoviral virus expressing β-galactosidase on the treated corneal surface for 30 minutes, extensive β-galactosidase expression was noted in the corneal epithelial cells of treated rats. Similarly, the specification teaches that upon injecting a recombinant replication-deficient adenovirus expressing β-galactosidase into the anterior chamber of the eye, positive staining for the majority of cells lining the posterior surface of the cornea or the corneal endothelial cells was observed for treated rats. Upon injection of the same recombinant adenovirus into the vitreous humor of the eye of treated rats, positive staining for some of the cells of the choroid (a vascular coat surrounding the posterior part of the eye) was detected, indicating β-galactosidase expression in those cells.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant claimed invention that is drawn to methods of treating an ocular wound simply by directly contacting an exogenous nucleic acid and an ocular cell *in situ* under suitable conditions so that the exogenous nucleic acid is expressed in the contacted ocular cell, for the following reasons.

(1) The state and the unpredictability of the art.

The nature of the instant claimed invention falls within the realm of gene therapy. The specification is not enabled for the instant invention because at the effective filing date of the present application (October 31, 1994), gene therapy was an immature and highly unpredictable art. This is supported by the report of Orkin et al. (Report and recommendations of the panel to assess the NIH investment in Research on gene therapy, pages 1-40, 1995) to the Director of NIH on the status of gene therapy. The report states "While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA advisory Committee (RAC)-approved protocols", and "Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and "Interpretation of the results of many gene therapy protocols has been hindered by a very low frequency of gene transfer, reliance on qualitative rather than quantitative assessments of gene transfer and expression, lack of suitable controls, and lack of rigorously defined biochemical or disease endpoints" (See pages 1-2 of the report). Even many years after the effective filing date of the present application, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) still state "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further

advancement to make gene therapy a reality" (page 471, col. 1, last sentence of first paragraph). It has been noted that there are several factors limiting an effective gene therapy, and these include suboptimal vectors, a lack of a stable *in vivo* transgene expression, and an efficient gene delivery to target tissues or cells. This indicates that obtaining therapeutic effects (for this instance wound healing effects) through a gene therapy approach was unpredictable even in 1999, let alone in 1994.

(2) The breadth of the claims.

The broad claims encompass treating an ocular wound (including an ocular wound after surgery or as a result of any ocular disease or any ocular infection) anywhere in the eye and that a broad scope of treating includes the reversion of an injured ocular cell or tissue to its original state by simply directly contacting any exogenous nucleic acid and any ocular cell (e.g., cells of the lens, the cornea, the iris, the retina, choroids, sclera, ciliary body, ocular muscle cells, optic nerve, ocular sensory, motor and autonomic nerves) under suitable conditions so that the ocular cell expresses the exogenous nucleic acid and whereby the ocular wound is treated.

(3) The amount of direction or guidance presented.

The instant specification is not enabled for such a claimed invention. Apart from the exemplification showing the expression of β-galactosidase in corneal epithelial cells, corneal endothelial cells and some of the cells of the choroids, the present disclosure fails to provide any evidence indicating that any therapeutic effects could be achieved for healing any ocular wound, particularly in light of the unpredictable attainment of any therapeutic effects via gene therapy at the effective filing date of the present application

as discussed above. The specification fails to provide any specific guidance and any relevant *in vivo* example (part of guidance) demonstrating that any beneficial wound healing effect (e.g., accelerating the ocular wound healing process or alleviating symptoms associated with an ocular wound) has been attained anywhere in the eye. In addition to the unpredictability of the gene therapy art, modulating the wound healing process to attain beneficial therapeutic effect is not routine because the wound healing process involves many complex molecular and cellular events, such as the inflammatory, proliferative and the remodeling phases requiring different cell types (neutrophils, monocytes, macrophages, fibroblasts as well as endothelial cells) in a spatial and temporal manner (Cordeiro et al., Br. J. Ophthalmol. 83:1219-1224, 1999). On the basis of the instant disclosure, apart from a cursory teaching of using transforming growth factor β (TGF-β) in corneal epithelial wounds (see specification on page 15, lines 14-15), it is unclear what other proteins would be useful in the treatment of ocular wounds, and to which ocular cell populations should an exogenous nucleic acid encoding TGF-β should be contacted in order to attain the desired therapeutic effects for treating an ocular wound anywhere in the eye given a diversity of tissues and cell types in the eye. There is also no evidence in the present application or in the prior art at the effective filing date of the present application, indicating or suggesting that TGF-β could be a "master therapeutic protein" for treating any ocular wound anywhere in the eye simply by being expressed in any ocular cell population. Additionally, it is uncertain whether an effective expression level of TGF-β could be attained in the desired ocular cell population, and whether TGF-β expression could be restricted only to

the desired ocular cell population. As discussed previously, a low frequency of gene transfer and expression as well as the lack of *in vivo* vector targeting are some of the factors contributing to the unpredictability in attaining therapeutic effects via gene therapy. Moreover, even in the case of TGF-β expression in ocular cells, the instant specification offers no guidance on how to control such expression, such that an inappropriate expression of TGF-β would not occur and result in the scarring and degeneration of ocular tissues which would defeat the therapeutic effects contemplated by Applicant. With the lack of sufficient guidance provided by the present disclosure for a skilled artisan on the numerous issues discussed immediately above, the simple qualitative β-galactosidase expression detected in various ocular cell populations is not reasonably correlated to the therapeutic effects contemplated by Applicant for treating any ocular wound, and therefore it would have required undue experimentation for a skilled artisan to make and use the instantly claimed invention.

Moreover, the physiological art is also recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of guidance and examples provided by the instant specification regarding to the issues set forth above, the unpredictable nature of the

gene therapy art as well as complexity of the wound-healing process, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the claimed invention at the effective filing date of the present application.

Responses to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on July 28, 2003 (pages 3-8) have been fully considered, but they are respectfully found to be unpersuasive.

(1) Applicant argues that the teachings of the instant specification are enabled as evidenced by the post-filing art of Bennett et al. (Photoreceptor cell rescue in retinal degeneration (rd) mice by *in vivo* gene therapy, Nature Medicine 2:649-654, 1996). Bennett et al. demonstrated that subretinal injection of Ad.CMVβPDE (a replication-defective adenovirus that contains the murine cDNA for wild-type β-subunit of the cGMP phosphodiesterase gene) results in βPDE transcripts and increased PDE activity and delays photoreceptor cell death by six weeks in retinal degeneration (*rd*) mice. As the system taught by Bennett et al. is very similar to the system described in the present application (e.g., recombinant Ad5 adenovirus which has the CMV/β galactosidase construction, 2×10^6 pfu was applied in several ways in the examples), the specification does indeed provide therapeutic effect or benefit. Applicant further argues that the efficiency of gene transfer is not required for the patentability of the present invention, and the references cited by Examiner discuss the difficulties associated with the attempt

to find generalized gene therapy techniques, and that Applicant does not purport to enable all fields of gene therapy, merely gene therapy for ocular tissues.

The results obtained in the post-filing art of Bennett et al. are irrelevant and are not correlated with the therapeutic effects contemplated by Applicant in the treatment of any ocular wound of the presently claimed invention. This is because there is no explicit teaching in the present disclosure for a subretinal injection of Ad.CMVβPDE at the dosage of 1 x 10^8 pfu to obtain the therapeutic effects observed by Bennett et al. Applicant is invited to point out the specific page number, and line number where such specific teachings are provided. Furthermore, Bennett et al. do not teach a method for obtaining any therapeutic effects in treating any ocular wound, including an ocular wound after surgery or a corneal epithelial wound or a corneal ulceration, or a method for utilizing a nucleic acid encoding a TGF-beta for obtaining the therapeutic effects contemplated by Applicant. Moreover, it should be noted that at the effective filing date of the present application, the attainment of any therapeutic effects via gene therapy was highly unpredictable as evidenced by the cited references on the state of the gene therapy art. It is clear from the report of Orkin et al. that at the effective filing date of the present application, clinical efficacy (implying the attainment of therapeutic effects) had not been definitely demonstrated in any gene therapy protocol (including gene therapy in ocular tissues). There are several factors limiting an effective gene therapy, and these include: suboptimal vectors, a lack of a stable *in vivo* transgene expression, and an efficient gene delivery to target tissues or cells as noted by Dang et al. The same factors are also involved in gene therapy for ocular diseases as supported by Bennett et

al. (Mol. Ther. 1:501-505, 2000, Cited previously) who state that "**As with any gene therapy experiment, success in the eye is dictated by the ability to efficiently transfer genetic material to target cells and to achieve long-term expression at appropriate levels**" (page 501, col. 2, middle of first paragraph). Dang et al further noted that there was a need for further advancement in many fields to make gene therapy a reality, indicating that the attainment of therapeutic effects (for this instance wound healing effects) through a gene therapy approach was unpredictable even in 1999, let alone in 1994.

(2) Applicant cited the references of Roberts et al., Massague, Smiddy et al. and Glaser et al. to illustrate that it was well known in the art that TGF-β could be used in the treatment of ocular wounds.

Firstly, none of these references teaches the attainment of therapeutic effects in the treatment of ocular wounds via gene therapy.

Secondly, Examiner noted that Glaser et al. obtained improved visual acuity in eyes with a full thickness macular hole only within an effective dose range of between 330 ng to 1330 ng of TGF-β_2 (page 1163, col. 2, first full paragraph). Smiddy et al. also observed positive chorioretinal wound healing effects only at the applied TGF-β dose concentrations of 70-700 ng (page 578, col. 3, first full paragraph). The simple detection of the β-galactosidase expression in corneal epithelial cells, corneal endothelial cells and in some of the cells of the choroids in the present specification is not an indication that effective TGF-β levels or effective levels of any other proteins

useful for wound healings have been expressed in ocular cells to yield the wound treatment effects desired by Applicant. There is no evidence of record either in the instant specification or in the prior art *in vivo* transgene expression can be properly controlled to desired therapeutic levels. It should be noted that an inappropriate expression of TGF-β would result in either no therapeutic effects or excessive fibrosis resulting in scarring and degeneration of ocular tissues as well as excessive formation of new blood vessels that defeat the purpose of achieving desired wound treatment effects. Massague et al. state "A localized excess of TGF-β activity in tissue could lead to an unbalanced deposition of extracellular matrix and contribute to a variety of fibrotic disorders. A case in point is the condition known as proliferative vitreoretinopathy (PVR). PVR occurs in 10% of eyes that undergo surgery for retinal detachment, and it leads to excessive intraocular fibrosis and blindness" (page 617, third full paragraph).

Thirdly, apart from a cursory teaching of using transforming growth factor β (TGF-β) in corneal epithelial wounds (see specification on page 15, lines 14-15), neither the instant specification nor the provided arts teach any other proteins that would be useful in the treatment of ocular wounds. Nor is there any evidence of record indicating that an effective level of TGF-β expressed in any ocular cell population could be used for treating an ocular wound at another location in the eye as clearly encompassed by the breadth of the claims.

(3) Applicant argues that the specification provides a road map for practicing the presently claimed invention, including the conditions used for the cellular uptake of specific forms of exogenous nucleic acids, the successful introduction of exogenous

nucleic acid into many types of ocular cells including corneal epithelial cells, corneal endothelial cells, cells of the tracecular meshwork, choroids cells, particularly example 1 showing the successful introduction of exogenous nucleic acid into ocular cells following surgical injury inflicted on a rat's eye, and that the conditions well known to those skill in the art that relate to *in vitro* uptake can be applied to *in vivo* ocular cells.

The general guidance provided by the instant specification as well as the detection of β-galactosidase in certain ocular cell populations are not deemed to be sufficient guidance for a skilled artisan to attain any ocular wound therapeutic effect in the methods as claimed for the reasons already set forth above, particularly in light of the state and the unpredictability of the gene therapy art for obtaining any therapeutic effects.

Accordingly, claims 23-24 and new claims 25-27 remain rejected under 35 U.S.C. 112, first paragraph.

Conclusions

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

JAMES KETTER
PRIMARY EXAMINER